Exhibit I

CURRICULUM VITAE

Name: Hisako YAMAMURA

Gender: Female

Registered Address: Nara prefecture

Date of Birth (Age) : June 25, 1949 (56)

Present Address: 151 Koyodai, Ikoma-shi, Nara prefecture

Tel: 0743-74-9165

Education Background, Career, Qualification

Education Background:

April 1965: Entered into Osaka Prefectural Otemae High School

March 1968: Graduated from Osaka Prefectural Otemae High School

April 1968: Entered into Osaka University, School of Pharmaceutical Sciences, Faculty of Pharmaceutical Chemistry

March 1972: Graduated from Osaka University, School of Pharmaceutical Sciences, Faculty of Pharmaceutical Chemistry

Career:

April 1972:

Joined Osaka Prefectural Government (Local Government Employee, senior official, specialized in Pharmaceutical Sciences)

Osaka Medical Center for Cancer and Cardiovascular Disease, Second Tumor Biochemistry Division

April 1978:

Osaka Medical Center for Cancer and Cardiovascular Disease, Research Center, Digestive Tumor/Cancer Inhibition Division

April 1995:

Osaka Medical Center for Cancer and Cardiovascular Disease, Research Center, Circulatory Biochemistry Division (Project General Manager: Katsuhito Takahashi)

From April 1999:

Teaching and Research guidance in Graduate School of Pharmaceutical Science, Osaka University, Life and Environmental Sciences, Clinical & Environmental Pathophysiology Session (1) (Assistant Professor: Katsuhito Takahashi)

Teaching of the following Master's thesis of Master course:

2001:

1. Preparation of Cre-transgenic mouse using a SM22α gene promoter

2. Functional Analysis of mouse calponin h2 gene using a transgenic mouse

2002:

1. Preparation of a cell-selective and replicable herpes simplex virus vector having a calponin promoter, and application thereof to cancer gene therapy

2. Preparation of a double deficient mouse for calponin and p53 gene, and functional analysis thereof

3. Expression of calponin in a cyprinodont vessel and gene cloning

2003:

1. Preclinical safety test of a cell-selective and replicable simplex herpes vector

2004

1. Preclinical animal test of a cancer-destructive herpes virus

2005

1. Tumor vessel maturing inhibition caused by deletion of calponin gene and anti-tumor effect of anti-VEGF antibody

Teaching of the following Master's thesis of Doctor course:
2003:
1. Investigation of the effectiveness of a drug having vasodilation effect to a heart failure patient
2006, present
In charge of teaching/research guidance of 2 graduates of Master Course

Was also in charge of teaching/research guidance of 3 doctor thesis of Graduate School of Medicine; 2 doctor thesis of Graduate School of Medical Dentistry; 1 doctor thesis of Graduate School of Sciences, 3 doctor thesis of Graduate School of Engineering, during 2000 to 2006.

Since April 2002 to present:
Associate Director, Department of Moleculer Medicine & Pathophysiology, Osaka Medical Center for Cancer and Cardiovascular Diseases (Department Director: Katsuhito Takahashi) (Local Government Employee, senior official, transfer to be specialized in Chemical Sciences)

Since February 2005
Chief Supervising Pharmacist of Test Drugs of Osaka Medical Center for Cancer and Cardiovascular Diseases, Gene therapy division, clinical test "Clinical test for effectiveness and safety of herpes simplex virus Type I HF10 for recurrence of breast cancer"

During this time:
April 1997: earn a PhD. in Pharmacology, Osaka University
Researcher of Osaka University, School of Pharmaceutical Sciences
(Graduate School of Pharmaceutical Science, Life and Environmental Sciences, Microorganism kinetics session)
"Molecular genetics of vascular smooth muscles"
March 1999: Finished the above

Degree: Doctor of Pharmacology
(Osaka University, Certificate No. 14249)
Acquisition date: February 3, 1999

License of Pharmacist
Registration Number: No. 135114
Acquisition date: January 24, 1973

Certified Pharmacist by Japan Pharmacists Education Center
Registration Number: NO. 04-11684
Acquisition date: November 7, 2003

Public Health Laboratory Technologist
Registration Number: No. 12424
Acquisition date: August 28, 1972

Medical Laboratory Technologist
Registration Number: No. 45020
Acquisition date: December 4, 1976

American Society of Gene Therapy

Finished "Comprehensive review course on clinical gene introduction"

Acquisition date: June 6, 2002

Activity in academic society

(membership, position of academic society)

1972, Member of Japanese Cancer Association

1973, Member of the Japanese Society of Gastroenterology

2000, Member of Japanese Society of Circulation Research

2000, Member of American Society of Gene Therapy

2002, Member of the Japan Society of Gene Therapy

2002, American Society of Gene Therapy

2003, Member of the Japan Society of Human Genetics

2003, Member of the Japanese Society for Virology

2005, Member of Japan Society of Obstetrics and Gynecology

2005, Member of the Pharmaceutical Society of Japan

Reward and Punishment

Award-winning, Society Prize, etc.

1979, Research Encouragement Award, Osaka Cancer Society

2000, Society Award (Asahi Award), the Japanese Society for Circulation Research

2002, Best thesis award, Japanese Association of Preventive medicine for Adult Disease

2003, Research Aid Award, Princess Takamatsu Cancer Research Fund (researcher in charge)

2005, Excellent Subject Award, 57th General Meeting, Academic Lecture of Japan Society of Obstetrics and Gynecology (Coauthor)

Achievement in obtaining scientific research fund,

intellectual property, etc.

Scientific Research Fund

Year ending March 1997 – March 2000

Japan Science and Technology Agency (JST),

Pioneering research 21.

Research collaborator (Research representative: Katsuhito Takahashi)

"Novel intracellular molecule mechanism regulating tissue repair and organogenesis"

59,100,000 yen

Year ending March 1998 – March 1999

Ministry of Education, Culture, Sports, Science and Technology,

Fundamental research (C).

Researcher in charge (Research representative: Katsuhito Takahashi)

"Producing smooth muscle-specific mutant mouse by Cre/loxP targeting system"

3,300,000 yen

Year ending March 2000 – March 2001

Ministry of Education, Culture, Sports, Science and Technology,

Fundamental research (B).

Researcher in charge (Research representative: Katsuhito Takahashi)

"Development of novel osteogenic therapy by suppressing calponin gene"

12,800,000 yen

Year ending March 2001 – March 2002
Ministry of Health, Labor and Welfare,
Research division of "Fundamental and clinical research on gene therapies for cancers"
(Chief of the research division: Yasushi Kaneda, Professor of Osaka Univ.)
Members of the research division or a researcher in charge (Research representative: Katsuhito Takahashi))
2,800,000 yen

Year ending March 2001 – March 2003
Japan Science and Technology Agency (JST),
Fundamental research and development promotion program.
Researcher in charge (Research representative: Katsuhito Takahashi)
"Development of novel gene therapy for selective disruption of tumor vessels"
32,000,000 yen

Year ending March 2002
Ministry of Education, Culture, Sports, Science and Technology,
Research division of "Research on specific areas of cancer – Gene therapies"
(Chief of the research division: Yusuke Nakamura, Professor of Tokyo Univ.)
Members of the research division or a researcher in charge (Research representative: Katsuhito Takahashi))
6,000,000 yen

Year ending March 2002 – March 2003
Ministry of Education, Culture, Sports, Science and Technology,
Fundamental research (C).
Research representative: Hisako Yamamura
"Development of novel targeting – gene therapy for refractory sarcoma "
3,500,000 yen

Year ending March 2003 – March 2004
Ministry of Health, Labor and Welfare,
Research division of "Fundamental and clinical research on gene therapies for cancers"
(Chief of the research division: Yasushi Kaneda, Professor of Osaka Univ.)
Member of the research division or a researcher in charge (Research representative: Katsuhito Takahashi))
3,200,000 yen

Year ending March 2003 – March 2004
Ministry of Education, Culture, Sports, Science and Technology,
Fundamental research (B).
Researcher in charge (Research representative: Katsuhito Takahashi)
"Development of targeting – gene therapy using novel replicating/targeting expression vector for selective distruption of refractory sarcoma"
14,700,000 yen

Year ending March 2004 – March 2005
Ministry of Education, Culture, Sports, Science and Technology,
Fundamental research (C).
Research representative: Hisako Yamamura
"Targeting therapy for refractory sarcoma in human, using GM-CSF loading conditionally – replicating herpes virus"
3,500,000 yen

Year ending March 2005 – March 2006
Ministry of Education, Culture, Sports, Science and Technology,
Fundamental research (A).
Researcher in charge: Hisako Yamamura
(Research representative: Katsuhito Takahashi)
35,740,000 yen in sum total
"Decision of the whole structure of virus for targeted disruption of refractory sarcoma and seed/cell stock production toward clinical tests"

Year ending March 2005 – March 2006
Japan Science and Technology Agency (JST),
Test for obtaining a patent right A.
Researcher in charge: Hisako Yamamura
(Research representative: Katsuhito Takahashi)
65,000,000 yen in sum total
"Development of virus for targeted disruption of cancer cells"

Year ending March 2006 – March 2008
Scientific research fund in the area of Health, Labor and Welfare,
Researcher in charge: Hisako Yamamura

(Research representative: Katsuhito Takahashi)

110,890,000 yen in sum total

"Research on the production of seed stock and clinical lot of oncolytic virus vector for targeted disruption of sarcoma and malignant mesothelioma, and estimation of safety and efficacy thereof"

20 Representative Studies:

1. Takahashi K.and Yamamura H. Studies and perspectives of calponin in smooth muscle regulation and cancer gene therapy. ***Advances in Biophysics*** 37, 91-111, 2003

2. Morioka T., Koyama H., Yamamura H., Tanaka S., Fukumoto S., Emoto M., Mizuguchi H., Hayakawa T., Kojima I., Takahashi K. and Nishizawa Y. Role of H1-calponin in pancreatic AR42J cell differentiation into insulin-producing cells. ***Diabetes*** 52, 760-766, 2003

3. Sasaki Y., Yamamura H., Kawakami Y., Yamada T., Ohigashi H., Hiratsuka M., Kameyama M., Ishikawa O., Imaoka S., Ishiguro S. and Takahashi K. Expression of smooth muscle calponin in tumor vessels of human hepatocellular carcinoma and its possible association with prognosis. ***Cancer*** 94, 1777-1186, 2002

4. Yamamura H., Hashio M., Noguchi M., Sugenoya Y., Osakada M., Hirano N., Sasaki Y., Yoden T, Awata N., Araki N., Tatsuta M., Miyatake S. and Takahashi K. Identification of the transcriptional regulatory sequences of human calponin promoter and their use in targeting of a conditionally replicating herpes vector to malignant human soft tissue and bone tumors. ***Cancer Research*** 61, 3969-3977, 2001

5. Yamamura H., Ikeda W., Shibata N., Awata N. and Takahashi K. Structure and expression of calponin in arterial smooth muscle cells. In *Ischemic Heart*, (edited by Mochizuki S., Takeda N., Nagano M. Dhalla N.S.), 87-95, Kluwer Academic Publishers, 1998

6. Yamamura H., Yoshikawa H., Tatsuta M., Akedo H. and Takahashi K. Expression of the smooth muscle calponin gene in human osteosarcoma and its possible association with prognosis. ***International Journal of Cancer*** 79, 245-2501, 1998

7. Yamamura H., Masuda H., Ikeda W., Tokuyama T., Takagi M., Shibata N., Tatsuta M. and Takahashi K. Structure and expression of the human SM22α gene, assignment of the gene to chromosome 11, and repression of the promoter activity by cytosine DNA methylation.
Journal of Biochemistry 122, 157-167, 1997

8. Tatsuta M., Iishi H., Yamamura H., Baba M., Taniguchi H. Enhancement by prolonged administration of caerulein of experimental carcinogenesis induced by N-methyl-N'-nitro-N- nitrosoguanidine in rats stomach. ***Cancer Research*** 48, 6332-6335, 1988

9. Tatsuta M., Iishi H., Yamamura H., Baba M., Yamamoto R., Taniguchi H. Effect of cimetidine on Inhibition by tetragastrin of carcinogenesis induced by N-methyl-N'-nitro-N- nitrosoguanidine in Wistar rats. ***Cancer Research*** 48, 1591-1595, 1988

10. Tatsuta M., Iishi H., Yamamura H., Taniguchi H. Enhancement by propranol of the inhibitory effect of tetragastrin on gastric carcinogenesis induced by

N-methyl-N'-nitro-N- nitrosoguanidine in Wistar rats. ***Cancer Research*** 47, 111-114, 1987

11. Tatsuta M., Iishi, H. Ichii M., Noguchi S., Yamamura H., Taniguchi H. Effect of tetragastrin on the colonic mucosa of rats during intrarectal administration of N-methyl-N'-nitro-N-nitroso- guanidine. ***Cancer Research*** 46, 4539-4542, 1986

12. Masaharu Tatsuta, Hiroyasu Iishi, Makoto Ichii, Sanai Noguchi,Hisako Yamamura, Haruo Taniguchi. Effect of tetragastrin on the colonic mucosa of rats during intrarectal administration of N-methyl-N'-nitro-N-nitrosoguanidine. ***Cancer Res.*** 46, 4539-4542,1986

13. Masaharu Tatsuta, Hiroyasu Iishi, Makoto Ichii, Sanai Noguchi, Hisako Yamamura, Haruo Taniguchi. Inhibitory effects of tetragastrin and histamine on carcinogenesis in the small intestines of Wistar rats by N-methyl-N'-nitro-N-nitrosoguanidine. ***J.Natl.Cancer Inst.*** 76, 277-281, 1986

14. Masaharu Tatsuta, Hisako Yamamura, Hiroyasu Iishi, Makoto Ichii, Sanai Noguchi, Miyako Baba, Haruo Taniguchi. Effect of a chemically defined diet in liquid form on colon carcinogenesis in rats. ***J.Natl.Cancer Inst.*** 75, 911-916, 1986

15. Tatsuta M., Yamamura H., Iishi H., Ichii M., Noguchi S., Baba M., Taniguchi H. Promotion by vagotomy of gastric carcinogenesis induced by N-methyl- N'-nitro-N-nitrosoguanidine in Wistar rats. ***Cancer Research*** 45, 94-197, 1985

16. Masaharu Tatsuta, Reiko Yamamoto, Hisako Yamamura, Hiroyasu Iishi, Sanai Noguchi, Makoto Ichii, Shigeru Okuda. Photodynamic effects of exposure to hematoporphyrin derivatives and dye-laser radiation on human gastric adenocarcinoma cells. ***J.Natl.Cancer Inst.*** 73, 59-67, 1984

17. Masaharu Tatsuta, Hisako Yamamura, Makoto Ichii, Haruo Taniguchi. Promotion by histamine of carcinogenesis in the forestomach and protection by histamine against carcinogenesis induced by N-methyl-N'-nitro-N- nitrosoguanidine in the glandular stomach in Wistar rats. ***J.Natl.Cancer Inst.*** 71, 361-364, 1983

18. Masaharu Tatsuta, Hisako Yamamura, Makoto Ichii, Haruo Taniguchi. Effect of prolonged administration of gastrin on experimental carcinogenesis in rat colon induced by intrarectal instilation of N-methyl-N'-nitro-N -nitrosoguanidine. ***Cancer Res.*** 43, 2258-2260, 1983

19. Masaharu Tatsuta, Hisako Yamamura, Haruo Taniguchi, Hiroshi Tamura. Gastrin protection against chemically induced gastric adenocarcinoma in Wistar rats: histpathology of the glandular stomach and incidence of gastric adenocarcinoma. ***J.Natl.Cancer Inst.*** 69, 59-66, 1982

20. Masaharu Tatsuta, Tadao Itoh, Shigeru Okuda, Hiroshi Tamura, Miyako Baba, Hisako Yamamura.Inhibition of gastrin secretion by pirenzepine (LS 519) in treatment of gastric ulcer. ***Scand. J. Gastroenterol.*** 16, 269-271, 1981

The above statement is true and correct.

July 21, 2006

Hisako Yamamura

略　歴

ふりがな	やまむら　ひさこ	男・女	本籍地	奈良　都道府県
氏名	山村　倫子			
生年月日（年齢）	昭和24年6月25日（56歳）		現住所	奈良県生駒市光陽台151 TEL 0743-74-9165

学　歴　・　職　歴　・　資格

（年　月　日）　（事　項）

学　歴

自：昭和40年4月　大阪府立大手前高等学校　入学
至：昭和43年3月　大阪府立大手前高等学校　卒業

自：昭和43年4月　大阪大学薬学部製薬化学科　入学
至：昭和47年3月　大阪大学薬学部製薬化学科　卒業

職　歴

自：昭和47年4月　大阪府入庁（地方公務員上級　薬学職）
大阪府立成人病センター　第Ⅱ腫瘍生化学部門
自：昭和53年4月　大阪府立成人病センター　研究所消化器腫瘍・免疫抑制部門
自：平成　7年4月　大阪府立成人病センター　研究所循環生化学部門（高橋克仁　主査）

自：平成11年4月　大阪大学大学院薬学研究科生命情報環境科学専攻　環境病因病態学（Ⅰ）講座（高橋克仁　助教授）において以下の教育・研究指導歴を有する
博士前期課程　指導修士論文
平成13年　1. SM22α遺伝子プロモーターを用いたCreトランスジェニクスマウスの作製
2. トランスジェニクスマウスを用いたマウスカルポニンh2遺伝子の機能解析
平成14年　1. カルポニンプロモーターをもつ細胞選択的複製可能型単純ヘルペスウイルスベクターの作製とがん遺伝子治療への応用
2. カルポニンおよびp53遺伝子二重欠失マウスの作成とその機能解析
3. メダカ血管におけるカルポニンの発現と遺伝子クローニング
平成15年　1. 細胞選択的複製可能型ヘルペスウイルスベクター　前臨床安全性試験
平成16年　1. がん結構ヘルペスウイルスの前臨床動物試験
平成17年　1. カルポニン遺伝子欠失による腫瘍血管成熟阻害とVEGF抗体の抗腫瘍効果　博士後期課程　指導博士論文
平成15年　1. 心不全患者に対する血管拡張作用を有する薬剤の有効性の検討
平成18年現在　博士前期課程学生　2名の教育・研究指導を担当中

他に平成12～18年　医学研究科博士論文3編、薬学研究科博士論文2編、理学研究科博士論文1編、工学研究科修士論文3編の教育・研究指導を担当

自：平成14年4月　大阪府立成人病センター研究所　病態生理学部門（高橋克仁部長）　主任研究員（地方公務員上級　化学研究職に移行）現在に至る

自：平成17年2月　大阪府立成人病センター遺伝子治療室臨床試験「再発乳がんに対する単純ヘルペスウイルス1型HF10の有効性、安全性に関する臨床試験」の試験薬管理責任薬剤師

この間
自：平成　9年4月　大阪大学薬学博士号を取得
大阪大学薬学部　研究生（薬学研究科生命情報環境科学専攻微生物動態学講座）「血管平滑筋の分子遺伝学」
至：平成11年3月　同上　修了

学　位	薬学博士（大阪大学　学位記 14249号）	取得年月日：平成11年2月3日
薬剤師免許	登録番号　第135114号	取得年月日：昭和48年1月24日
日本薬剤師研修センター認定薬剤師免許	登録番号　第04-11684　号	取得年月日：平成15年11月7日

衛生検査・技師免許	登録番号　：第12424号	取得年月日：昭和47年8月28日
臨床検査・技師免許	登録番号　：第45020号	取得年月日：昭和51年12月4日
米国遺伝子治療学会	臨床遺伝子導入包括的レビューコース修了認定	取得年月日：平成14年　6月6日

学会及び社会における活動等（所属学会・役職等）

昭和47年　日本癌学会　会員
昭和48年　日本消化器病学会　会員
平成12年　日本心臓管作動物質学会　会員
平成12年　アメリカ遺伝子治療学会　会員
平成14年　日本遺伝子治療学会　会員
平成14年　アメリカ遺伝子治療学会
平成15年　日本人類遺伝学会　会員
平成15年　日本ウイルス学会　会員
平成17年　日本産科婦人科学会　会員
平成17年　日本薬学会　会員

賞罰

受賞　学会賞　他
昭和　54年　大阪対がん協会研究奨励賞
平成　12年　日本心臓管作動物質学会　学会賞（述　賞）
平成　14年　成人病予防医学財団研究奨励　最優秀論文賞
平成　15年　高松宮妃癌研究基金研究助成賞（分担研究者）
平成　17年　第57回日本産婦人科学会総会・学術講演会　優秀演題賞（共同演者）

科学研究費・知的財産等取得実績

科学研究費

平成9年ー12年度
科学技術振興事業団（JST）　さきがけ研究21　研究総力者　（研究代表者　高橋克仁）
「組織修復と器官形成を制御する新しい細胞内分子機構」　5910万円

平成10年ー11年度
文部科学省　基盤研究（C）研究分担者　（研究代表者　高橋克仁）
「Cre/loxP ターゲティングシステムを用いた平滑筋特異的変異マウスの作成」　330万円

平成12年ー13年度
文部科学省　基盤研究（B）研究分担者　（研究代表者　高橋克仁）
「カルポニン遺伝子の抑制による新しい骨形成治療法の開発」　1280万円

平成13年ー14年度
厚生労働省「がんに対する遺伝子治療の基礎的および臨床的研究」研究班
（班長：金田　安史　大阪大学教授）班員 研究分担者　（研究代表者　高橋克仁））　280万円

平成13年ー15年度
科学技術振興事業団（JST）基礎的研究発展推進事業　研究分担者　（研究代表者　高橋克仁）
「腫瘍血管を選択的に破壊する新しい遺伝子治療法の開発」　3200万円

平成14年度
文部科学省「がん特定領域研究-遺伝子治療」研究班
（班長　中村　祐輔　東京大学教授）　班員 研究分担者　（研究代表者　高橋克仁）　600万円

平成１４－１５年度
文部科学省　基盤研究（C）研究代表者：山村　倫子
「難治性肉腫に対する新しい標的遺伝子治療法の開発」　３５０万円

平成１５年－１６年度
厚生労働省「がんに対する遺伝子治療の基礎的および臨床的研究」研究班
（班長：金田　安史　大阪大学教授）　班員 研究分担者　（研究代表者　高橋克仁）　３２０万円

平成１５年－１６年度
文部科学省　基盤研究（B）研究分担者（研究代表者　高橋克仁）
「難治性肉腫を選択的に破壊する新規複製・発現ベクターを用いた標的遺伝子療法の開発」
１４７０万円

平成１６年－１７年度
文部科学省　基盤研究（C）研究代表者：山村　倫子
「GM-CSF 搭載制限増殖型ヘルペスウイルスを用いたヒト難治性肉腫の標的治療」　３５０万円

平成１７年－１８年度
文部科学省　基盤研究（A）研究分担者：山村倫子（研究代表者　高橋克仁）総額３５７４万円
「臨床試験に向けた難治性肉腫標的破壊ウイルスの全構造決定とシードセルストックの作成」

平成１７年－１８年度
科学技術振興機構　橋渡し試験A　研究分担者　山村倫子（研究代表者：高橋克仁）総額６５００万円
「がん相応標的破壊ウイルスの開発」

平成１８年－２０年度
厚生労働科学研究費　研究分担者：山村倫子（研究代表者：高橋克仁）総額１億１０８９万円
「肉腫および悪性中皮腫を標的破壊する腫瘍溶解性ウイルスベクターのシードストックおよび臨床ロットの製造とその安全性・有効性評価に関する研究」

代表的な論文２０報

1 Takahashi K and Yamamura H. Studies and perspectives of calponin in smooth muscle regulation and cancer gene therapy. ***Advances in Biophysics*** 37, 91-111, 2003

2 Moroka T, Koyama H, Yamamura H, Tanaka S, Fukumoto S, Emoto M, Mizuguchi H, Hayakawa T, Kojima I, Takahashi K, and Nishizawa Y. Role of H1-calponin in pancreatic AR42J cell differentiation into insulin-producing cells. ***Diabetes*** 52, 760-766, 2003

3 Sasaki Y, Yamamura H, Kawakami Y, Yamada T, Ohgashi H, Hiratsuka M, Kameyama M, Ishikawa O, Imaoka S, Ishiguro S, and Takahashi K. Expression of smooth muscle calponin in tumor vessels of human hepatocellular carcinoma and its possible association with prognosis. ***Cancer*** 94, 1777-1786, 2002

4 Yamamura H, Hashio M, Noguchi M, Sugenoya Y, Osakada M, Hirano N, Sasaki Y, Yoden T, Awata N, Araki N, Tatsuta M, Miyatake S, and Takahashi K. Identification of the transcriptional regulatory sequences of human calponin promoter and their use in targeting of a conditionally replicating herpes vector to malignant human soft tissue and bone tumors. ***Cancer Research*** 61, 3969-3977, 2001

5 Yamamura H, Ikeda W, Shibata N, Awata N, and Takahashi K. Structure and expression of calponin in arterial smooth muscle cells. In *Ischemic Heart*. (edited by Mochizuki S, Takeda N, Nagano M, Dhalla N.S.), 87-95, Kluwer Academic Publishers, 1998

6. Yamamura H., Yoshikawa H., Tatsuta M., Akedo H. and Takahashi K. Expression of the smooth muscle calponin gene in human osteosarcoma and its possible association with prognosis *International Journal of Cancer* 79, 245-2501, 1998

7. Yamamura H., Masuda H., Ikeda W., Tokuyama T., Takagi M., Shibata N., Tatsuta M. and Takahashi K. Structure and expression of the human SM22α gene, assignment of the gene to chromosome 11, and repression of the promoter activity by cytosine DNA methylation. *Journal of Biochemistry* 122, 157-167, 1997

8. Tatsuta M., Iishi H., Yamamura H., Baba M., Taniguchi H. Enhancement by prolonged administration of cacrulein of experimental carcinogenesis induced by N-methyl-N'-nitro-N- nitrosoguanidine in rats stomach *Cancer Research* 48, 6332-6335, 1988

9. Tatsuta M., Iishi H., Yamamura H., Baba M., Yamamoto R., Taniguchi H. Effect of cimetidine on Inhibition by tetragastrin of carcinogenesis induced by N-methyl-N'-nitro-N- nitrosoguanidine in Wistar rats *Cancer Research* 48, 1591-1595, 1988

10. Tatsuta M., Iishi H., Yamamura H., Taniguchi H. Enhancement by propranol of the inhibitory effect of tetragastrin on gastric carcinogenesis induced by N-methyl-N'-nitro-N- nitrosoguanidine in Wistar rats *Cancer Research* 47, 111-114, 1987

11. Tatsuta M., Iishi, H. Ichii M., Noguchi S., Yamamura H., Taniguchi H. Effect of tetragastrin on the colonic mucosa of rats during intrarectal administration of N-methyl-N'-nitro-N-nitroso- guanidine *Cancer Research* 46, 4539-4542, 1986

12. Masaharu Tatsuta, Hiroyasu Iishi, Makoto Ichii, Sanai Noguchi,Hisako Yamamura, Haruo Taniguchi Effect of tetragastrin on the colonic mucosa of rats during intrarectal administration of N-methyl-N'-nitro-N-nitrosoguanidine. *Cancer Res.* 46, 4539-4542,1986

13. Masaharu Tatsuta, Hiroyasu Iishi, Makoto Ichii, Sanai Noguchi, Hisako Yamamura, Haruo Taniguchi Inhibitory effects of tetragastrin and histamine on carcinogenesis in the small intestines of Wistar rats by N-methyl-N'-nitro-N-nitrosoguanidine. *J.Natl.Cancer Inst.* 76, 277-281, 1986

14. Masaharu Tatsuta, Hisako Yamamura, Hiroyasu Iishi, Makoto Ichii, Sanai Noguchi, Miyako Baba, Haruo Taniguchi Effect of a chemically defined diet in liquid form on colon carcinogenesis in rats *J.Natl.Cancer Inst.* 75, 911-916, 1986

15. Tatsuta M., Yamamura H., Iishi H., Ichii M., Noguchi S., Baba M., Taniguchi H. Promotion by vagotomy of gastric carcinogenesis induced by N-methyl- N'-nitro-N- nitrosoguanidine in Wistar rats *Cancer Research* 45, 94-197, 1985

16. Masaharu Tatsuta, Reiko Yamamoto, Hisako Yamamura, Hiroyasu Iishi, Sanai Noguchi, Makoto Ichii, Shigeru Okuda Photodynamic effects of exposure to hematoporphyrin derivatives and dye-laser radiation on human gastric adenocarcinoma cells *J.Natl.Cancer Inst.* 73, 59-67, 1984

17. Masaharu Tatsuta, Hisako Yamamura, Makoto Ichii, Haruo Taniguchi Promotion by histamine of carcinogenesis in the forestomach and protection by histamine against carcinogenesis induced by N-methyl-N'-nitro-N- nitrosoguanidine in the glandular stomach in Wistar rats *J.Natl.Cancer Inst.* 71, 361-364, 1983

18. Masaharu Tatsuta, Hisako Yamamura, Makoto Ichii, Haruo Taniguchi Effect of prolonged administration of gastrin on experimental carcinogenesis in rat colon induced by intrarectal instilation of N-methyl-N'-nitro-N -nitrosoguanidine *Cancer Res.* 43, 2258-2260, 1983

19. Masaharu Tatsuta, Hisako Yamamura, Haruo Taniguchi, Hiroshi Tamura Gastrin protection against chemically induced gastric adenocarcinoma in Wistar rats: histpathology of the glandular stomach and incidence of gastric adenocarcinoma. *J.Natl.Cancer Inst.* 69, 59-66, 1982

20. Masaharu Tatsuta, Tadao Itoh, Shigeru Okuda, Hiroshi Tamura, Miyako Baba, Hisako Yamamura Inhibition of gastrin secretion by pirenzepine (LS 519) in treatment of gastric ulcer. *Scand. J.*

Gastroenterol. 16, 269-271, 1981

上記のとおり相違ありません

平成 18年 7月 21日

氏名 山村倫子 (自署名)
(Hisako Yamamura)

DECLARATION

I, Hisako Yamamura, PH. D. of Osaka Medical Center for Cancer and Cardiovascular Diseases located at 1-3-3 Nakamichi, Higashinari-ku, Osaka City, Osaka, Japan hereby faithfully declares and states that:

1. I was born in Osaka on June 25, 1949. After completing academic study at Faculty of Pharmaceutical Chemistry, School of Pharmaceutical Science, Osaka University in 1972, I joined Osaka Medical Center for Cancer and Cardiovascular Diseases and was a research fellow at the Gastral Tumor Laboratory from 1972. I have been serving as an associate director at the Department of Molecular Medicine & Pathophysiology since 2001.

2. My major field of research is Cancer Gene Therapy. A curriculum vitae for me is attached hereto as Exhibit I along with the list of literatures including my academic works for recent 20 years.

3. As is seen from my curriculum vitae, I am a member of Japanese Cancer Association. To my contribution in Gene therapy for smooth muscle cells, I was awarded Research Encouragement Award, Osaka Cancer Society in 1979, Society Award (Asahi Award), the Japanese Society for Circulation Research in 2000, Best thesis award, Japanese Association of Preventive medicine for Adult Disease in 2002, Research Aid Award, Princess Takamatsu Cancer Research Fund in 2003, Excellent Subject Award, 57th General Meeting, Academic Lecture of Japan Society of Obstetrics and Gynecology in 2005.

4. I am also a director of the alumni association of School of Pharmaceutical Science, Osaka University.

5. I was asked to consider the following points:

Office Action for US patent application serial No. 10/500,173 "Cell-Specific Expression/Replication Vector" of which I am one of the applicants was issued by USPTO on April 21, 2006. In the Office Action the examiner states that the present invention is obvious over the following references under 35 U.S.C. § 103(a), and I was asked to review that the present invention was not obvious over the references below.

According to the Examiner, the claimed invention is obvious over Martuza (U.S. Patent 5,728,379) in view of Yamamura (Cancer Res 61: 3969-3977). In this regard, I respectfully submit as follows. There are two ways to make a oncolytic herpesvirus vector that comprises ICP4 gene having a cell-specific promoter linked thereto and that proliferates in a specific human malignant tumor; one is to delete thymidine kinase (TK), the other is to delete ribonucleotide reductase. If TK is deleted, such vector cannot be expected to be clinically applied from the viewpoint of safety.

Martuza used the method to delete TK via homologous recombination. This was because TK-deficient recombinants could be easily selected by using the property of ganciclovir or aciclovir to suppress proliferation of non-recombinants having TK. On the other hand, a method for accurately performing homologous recombination of ICP4 gene that is linked to a cell-specific promoter at the ribonucleotide reductase locus while preserving endogenous TK, was never succeeded in view of the level of the art of that time, by Martuza and his co-inventors, Rabkin, Miyatake in US 5,728,379, since selection of TK-deficient recombinants using ganciclovir or aciclovir as described above was impossible. We are the first inventors who performed the separation of the ribonucleotide reductase deletion mutants having ICP4 gene linked to a cell-specific promoter, with the use of a method described in claim 35 of the present invention.

Although Martuza suggested deleting ribonucleotide reductase in US 5,728,379, it was not until 2005 that Martuza et al. succeeded in producing a herpesvirus vector deleting ribonucleotide reductase that has ICP4 gene linked to a cell-specific promoter via a method for producing a gene recombinant with the use of "bacterial artificial chromosome (BAC) –based system" developed in 2003 by Saeki Y. et al. This is obvious from the disclosure in ONCOLYTIC VIRUSES AS CANCER THERAPEUTICS (March 6-13,2005)" (See Exhibit II).

For the reasons mentioned above, I respectfully submit that the present invention could not have been achieved in 2002 when the present application was filed, even by the most skilled experts at that time for herpesvirus gene recombination including Martuza himself and his co-inventors, by combining Martuza (U.S. Patent 5,728,379) and Yamamura (Cancer Res 61: 3969-3977).

Hisako Yamamura, Ph. D.

Date this 21 day of July, 2006

Declaration

（宣誓供述書）

私、日本国大阪府大阪市東成区中道１丁目３の３に所在する大阪府立成人病センターに所属する田村俊子は、厳粛かつ誠実に次のように供述いたします

１．私は、１９４９年６月２５日に大阪府で生まれ、１９７２年に大阪大学薬学部製薬化学科を終了した後、大阪府立成人病センターに所属し、１９７２年より消化器腫瘍研究室研究員を経て、２００１年より研究所病態生理学部門主任研究員であり、現在に至ります

２．私の主な研究領域は、Cancer Gene Therapy です．私の経歴書を、私の最近２０年間の著作を含む文献リストとともに、本宣誓供述書に添付し、別紙１とします．

３．私の経歴書からもわかるように、私は Japanese Cancer Association の会員であります．私の Gene therapy for smooth muscle cells における貢献に対し、昭和５１年に大阪対がん協会研究奨励賞、平成１２年に日本心臓血管作動物質学会、学会賞（旭　賞）、平成１４年に成人病予防医学財団研究奨励　最優秀論文賞、平成１５年に高松宮妃癌研究基金研究助成賞、平成１７年に第５７回日本産婦人科学会総会・学術講演会優秀演題賞を受けました。

４．私は、大阪大学薬学部薬友会（同窓会）理事でもあります

５．私は下記の件につき検討をするよう、依頼を受けました。

私が出願人の１人であります米国特許出願第１０／５００１７３号「細胞特異的発現複製ベクター」に対し、米国特許商標庁からオフィスアクションが２００６年４月２１日に出されております．その中で、審査官殿は米国特許法第１０３条(a)に基づき本発明が下記文献に照らして自明であると認定されていますが、

本発明は、それら文献から決して自明ではないことを検討するよう、依頼を受けました。

審査官によりますと本発明は、Yamamura (Cancer Res 61: 3969-3977) と Martuza (US 5,728,379) とを合わせることにより自明であるとされていますが、細胞特異的なプロモーターを連結したICP4遺伝子をもち、特定のヒト悪性腫瘍で増殖する腫瘍溶解性（Oncolytic）ヘルペスウイルスベクターとしては、チミジンキナーゼ（TK）を欠失させるか、リボヌクレオチドリダクターゼを欠失させるかの２通りのやり方があります。TKが欠失していると、安全性の観点からヒトに対する臨床応用は期待できません。

Martuzaは相同組換え法を用いて、TKを欠失させる方法をとりました。それは、ガンシクロビルまたはアシクロビルがTKをもつ非組換え体の増殖を抑制するという性質を利用して、TK欠失の組換え体を選別することが容易にできたからであります。一方、内在性のTKを温存しつつ、リボヌクレオチドリダクターゼ遺伝子座に細胞特異的なプロモーターに連結したICP4遺伝子を正確に相同組換えするという方法は、上述のガンシクロビルまたはアシクロビルを用いたTK欠失組換え体の選別が不可能であるため、当時の技術水準ではMartuza及びUS 5,728,379においてMartuzaのco-inventorであったRabkin、Miyatakeを含めて、決して成功しませんでした。細胞特異的なプロモーターに連結したICP4遺伝子をもつリボヌクレオチドリダクターゼ欠失変異体の分離は、本発明において、クレーム３５の方法を用いることによって初めて我々が行ったものであります。

Martuzaは、リボヌクレオチドリダクターゼを欠落させることについて示唆だけはしていますが、彼らが細胞特異的なプロモーターに連結したICP4遺伝子をもつリボヌクレオチドリダクターゼを欠失させたヘルペスウイルスベクターの作製に成功したのは、２００３年にSaeki Y.らが開発した"bacterial artificial chromosome (BAC) -based system"を用いて遺伝子組換え体を作製する方法を初用して２００５年にはじめてなし得たことです。このことは、Martuzaらの"ONCOLYTIC VIRUSES AS CANCER THERAPEUTICS (March 6-13, 2005)"における発表（別紙１１）により明らかです。

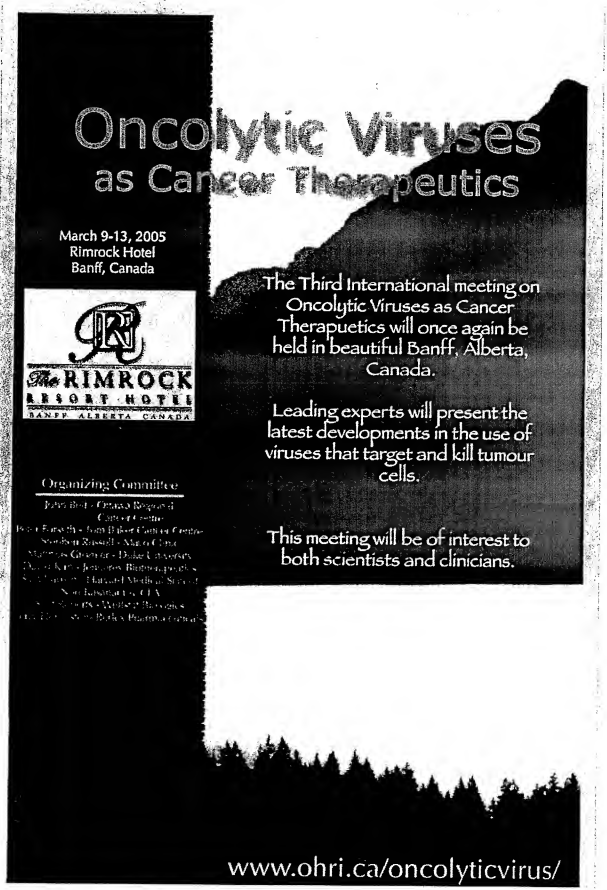
以上の理由により、本発明の出願当時である２００２年では、Yamamura (Cancer

Res 61: 3969-3977)とMartuza (US 5,728,379)とを合わせることにより本発明に到達することは、Martuza自身とその co-inventor を含めて、当時のヘルペスウイルスの遺伝子組換えに関する最高の技術水準をもつ専門家であっても不可能であったということを、ここに申し述べます。

（署名）　Hisako Yamamura, Ph.D.

山村倫子

日付：２００６年７月２１日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Abstracts of papers presented at the 2005 meeting on

ONCOLYTIC VIRUSES AS CANCER THERAPEUTICS

March 9-13th 2005

Arranged by:
John C. Bell – Ottawa Regional Caner Centre
Peter Forsyth – Tom Baker Cancer Centre
Stephen Russell – Mayo Clinic
Matthias Gromier – Duke University
David Kirn – Jennerex Biotherapeutics
Sam Rabkin – Harvard Medical School
Nori Kasahara – UCLA
Scot Roberts – Wellstat Biologics
Terry Hermiston – Berex Pharmaceuticals

This meeting was funded in part by the NCIC, ACB, CIHR and by Wellstat

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Alberta Cancer Board

National Cancer Institute of Canada

Institut national du cancer du Canada

Development of oncolytic herpes simplex virus (HSV) vector selectively replicating in colorectal cancer cells with highly activated beta-catenin/Wnt pathway.

Toshihiko Kuroda, Samuel Rabkin, Robert L. Martuza

Molecular Neurosurgery Laboratory, Massachusetts General Hospital, Charlestown, MA

Activation of Wnt/beta-catenin pathway is frequently observed in colorectal cancer cells. Here, we report the construction of an oncolytic HSV vector driven by beta-catenin/Wnt signaling and its effectiveness against colorectal cancer cells with a highly activated beta-catenin/Wnt pathway. We have developed a bacterial artificial chromosome (BAC)-based system for the construction of `transcriptionally targeted` oncolytic HSV. An HSV-BAC vector with deletions in both UL39 (ICP6) and alpha4 (ICP4) genes serves as the backbone plasmid in this system. The vector also contains loxP and FRT recombination sites. The ICP4 coding sequence driven by an exogenous enhancer/promoter on a loxP containing shuttle plasmid is inserted into the HSV-BAC by Cre recombinase. Subsequent treatment with FLPe recombinase removes the BAC sequences and generates an infectious HSV genome. The resultant recombinant HSV replicates only when the inserted ICP4 gene is transactivated by the exogenous promoter in infected cells. We also constructed an artificial promoter containing tandem repeats of the beta-catenin/Wnt responsive element and the human 4F2 heavy-chain transcriptional enhancer. In SW480 colon cancer cells, with an activated beta-catenin/Wnt pathway, this promoter construct had transcriptional activity even higher than the CMV promoter/enhancer in a luciferase reporter gene assay. This beta-catenin responsive promoter construct was used to drive ICP4 in a recombinant HSV vector, termed bM24TE. bM24TE efficiently killed SW480 cells at a MOI of 0.1 in vitro, whereas it showed minimal cytotoxicity on HeLa cells. In a single step growth assay bM24TE replicated in SW480 but not in HeLa cells. Oncolytic HSV vectors targeting the beta-catenin/Wnt pathway are a promising strategy to selectively kill tumor cells with activated beta-catenin.